4164-01-P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA-2018-N-3240]

List of Bulk Drug Substances for Which There is a Clinical Need Under Section 503B of the Federal Food, Drug, and Cosmetic Act

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA or Agency) is developing a list of bulk drug substances (active pharmaceutical ingredients) for which there is a clinical need (the 503B Bulks List). Drug products that outsourcing facilities compound using bulk drug substances on the 503B Bulks List qualify for certain exemptions from the Federal Food, Drug, and Cosmetic Act (FD&C Act) provided certain conditions are met. This notice identifies three bulk drug substances that FDA has considered and is proposing not to include on the list: bumetanide, nicardipine hydrochloride, and vasopressin. Additional bulk drug substances nominated by the public for inclusion on this list are currently under consideration and will be the subject of future notices.

DATES: Submit either electronic or written comments on the notice by [INSERT DATE 60 DAYS AFTER DATE OF PUBLICATION IN THE *FEDERAL REGISTER*] to ensure that the Agency considers your comment on this notice before it begins work on a notice reflecting the Agency's final decision about whether to include these substances on the 503B Bulks List.

ADDRESSES: You may submit comments at any time as follows:

Electronic Submissions

Submit electronic comments in the following way:

- Federal eRulemaking Portal: https://www.regulations.gov. Follow the instructions for submitting comments. Comments submitted electronically, including attachments, to https://www.regulations.gov will be posted to the docket unchanged. Because your comment will be made public, you are solely responsible for ensuring that your comment does not include any confidential information that you or a third party may not wish to be posted, such as medical information, your or anyone else's Social Security number, or confidential business information, such as a manufacturing process. Please note that if you include your name, contact information, or other information that identifies you in the body of your comments, that information will be posted on https://www.regulations.gov.
- If you want to submit a comment with confidential information that you do not wish to be made available to the public, submit the comment as a written/paper submission and in the manner detailed (see "Written/Paper Submissions" and "Instructions").

Written/Paper Submissions

Submit written/paper submissions as follows:

- Mail/Hand delivery/Courier (for written/paper submissions): Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852.
- For written/paper comments submitted to the Dockets Management Staff, FDA will post your comment, as well as any attachments, except for information submitted, marked and identified, as confidential, if submitted as detailed in "Instructions."

Instructions: All submissions received must include the Docket No. FDA-2018-N-3240 for "List of Bulk Drug Substances For Which There Is a Clinical Need Under Section 503B of the Federal Food, Drug, and Cosmetic Act." Received comments will be placed in the docket and, except for those submitted as "Confidential Submissions," publicly viewable at https://www.regulations.gov or at the Dockets Management Staff between 9 a.m. and 4 p.m., Monday through Friday.

- Confidential Submissions--To submit a comment with confidential information that you do not wish to be made publicly available, submit your comments only as a written/paper submission. You should submit two copies total. One copy will include the information you claim to be confidential with a heading or cover note that states "THIS DOCUMENT CONTAINS CONFIDENTIAL INFORMATION." The Agency will review this copy, including the claimed confidential information, in its consideration of comments. The second copy, which will have the claimed confidential information redacted/blacked out, will be available for public viewing and posted on https://www.regulations.gov. Submit both copies to the Dockets Management Staff. If you do not wish your name and contact information to be made publicly available, you can provide this information on the cover sheet and not in the body of your comments and you must identify this information as "confidential." Any information marked as "confidential" will not be disclosed except in accordance with 21 CFR 10.20 and other applicable disclosure law. For more information about FDA's posting of comments to public dockets, see 80 FR 56469, September 18, 2015, or access the information at: https://www.gpo.gov/fdsys/pkg/FR-2015-09-18/pdf/2015-23389.pdf.

Docket: For access to the docket to read background documents or the electronic and written/paper comments received, go to https://www.regulations.gov and insert the docket number, found in brackets in the heading of this document, into the "Search" box and follow the prompts and/or go to the Dockets Management Staff, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852.

FOR FURTHER INFORMATION CONTACT: Elizabeth Hankla, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 51, Rm. 5216, Silver Spring, MD 20993, 301-796-3110.

SUPPLEMENTARY INFORMATION:

I. Background

A. Drug Compounding

Compounded drug products can serve an important role for patients whose clinical needs cannot be met by FDA-approved drug products, such as patients who have an allergy and need a medication to be made without a certain inactive ingredient (e.g., a dye) or hospital inpatients who need infusions of a drug combined with a particular diluent. However, they also pose a higher risk to patients than FDA-approved drugs. In 2012, contaminated injectable drug products that a State-licensed compounding pharmacy shipped to patients and healthcare practitioners across the country caused a fungal meningitis outbreak that resulted in more than 60 deaths and 750 cases of infection.[1] This was the most serious of a long history of outbreaks and other serious adverse events, including overdoses, associated with contaminated, superpotent, or otherwise poor quality compounded drugs.

[1] See https://www.cdc.gov/HAI/outbreaks/meningitis.html.

In response to this outbreak, Congress enacted the Drug Quality and Security Act (Pub. L. 113-54), which, among other things, added new section 503B to the FD&C Act (21 U.S.C. 353b) and created a new category of compounders known as outsourcing facilities.[2] Drug products compounded by outsourcing facilities in accordance with the conditions of section 503B are exempt from FDA drug approval requirements and the requirement that they be labeled with adequate directions for use. Because compounded drug products are not FDA-approved, they have not undergone FDA premarket review for safety, effectiveness, and quality. Although outsourcing facilities must comply with current good manufacturing practice (CGMP) requirements and are inspected by FDA according to a risk-based schedule, their drug products have not been determined to be safe or effective for conditions of use reflected in drug product labeling and lack a premarket inspection and finding of manufacturing quality, all of which are part of the drug approval process. Because compounded drug products are subject to a lower regulatory standard than FDA-approved drug products, they should only be used by patients whose medical needs cannot be met by an FDA-approved drug product.

Outsourcing facilities sometimes compound drug products using bulk drug substances and other times using finished drug products as the starting materials. In general, compounding using bulk drug substances presents a greater risk to patients than compounding using FDA-approved drug products. FDA-approved drug products provide certain assurances not provided by bulk drug substances, including assurances associated with premarket review by FDA for

[2] See Pub. L. 113-54, section 102(a), 127 Stat. 587, 587-588 (2013). Other compounders, which are not the subject of this notice, are regulated under section 503A of the FD&C Act (21 U.S.C. 353a). These include licensed pharmacists in State-licensed pharmacies or Federal facilities, and licensed physicians, who have not registered an outsourcing facility with FDA. D rug products compounded by section 503A compounders are exempt from sections 505 (new drug approval requirements), 502(f)(1) (labeling with adequate directions for use), and 501(a)(2)(B) (CGMP requirements) if the conditions of section 503A are met, including that compounding is based on the receipt of valid prescriptions for identified individual patients (section 503A(a)). In general, section 503A compounders do not register with and are not routinely inspected by FDA, and they are primarily overseen by the States.

safety, effectiveness, and quality. Further, using a bulk drug substance in compounding when an FDA-approved drug product would be suitable would undermine the premarket approval process by reducing the incentive for applicants to invest in and seek FDA approval of drug products. The drug approval process is critical to ensure patient access to pharmaceuticals whose quality, safety, and effectiveness have been established.

The conditions that section 503B of the FD&C Act places on compounding by outsourcing facilities, including conditions on compounding using bulk drug substances, help to mitigate the risks associated with compounded drug products and protect patient health. Among these is the condition that directs FDA to place a bulk drug substance on the list of bulk drug substances that outsourcing facilities can use in compounding (503B Bulks List) only if there is a clinical need for outsourcing facilities to compound drug products using the bulk drug substance.

B. Statutory and Regulatory Background

Section 503B of the FD&C Act describes the conditions that must be satisfied for drug products compounded by an outsourcing facility to be exempt from section 505 (21 U.S.C. 355) (concerning the approval of drugs under new drug applications (NDAs) or abbreviated new drug applications (ANDAs)); section 502(f)(1) (21 U.S.C. 352(f)(1)) (concerning the labeling of drugs with adequate directions for use); and section 582 (21 U.S.C. 360eee-1) (concerning drug supply chain security requirements).[3]

Drug products compounded under the conditions in section 503B are not exempt from CGMP requirements in section 501(a)(2)(B) of the FD&C Act (21 U.S.C. 351(a)(2)(B)).[4] Outsourcing facilities are also subject to FDA inspections according to a risk-based schedule,

[3] Section 503B(a) of the FD&C Act.
[4] Compare section 503A(a) of the FD&C Act (exempting drugs compounded in accordance with that section) with section 503B(a) of the FD&C Act (not providing the exemption from CGMP requirements).

specific adverse event reporting requirements, and other conditions that help to mitigate the risks of the drug products they compound.[5] Outsourcing facilities may or may not obtain prescriptions for identified individual patients and can, therefore, distribute compounded drugs to healthcare practitioners for "office stock," to hold in their offices in advance of patient need.[6]

One of the conditions that must be met for a drug product compounded by an outsourcing facility to qualify for exemptions under section 503B is that the outsourcing facility may not compound a drug using a bulk drug substance unless (a) the bulk drug substance appears on a list established by the Secretary identifying bulk drug substances for which there is a clinical need (the 503B Bulks List); or (b) the drug compounded from such bulk drug substances appears on the drug shortage list in effect under section 506E of the FD&C Act (FDA's drug shortage list) (21 U.S.C. 356e) at the time of compounding, distribution, and dispensing.[7]

For purposes of section 503B, *bulk drug substance* means an active pharmaceutical ingredient as defined in 21 CFR 207.1(b).[8] *Active pharmaceutical ingredient* means any substance that is intended for incorporation into a finished drug product and is intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease, or to affect the structure or any function of the body, but the term does not include intermediates used in the synthesis of the substance.[9,10]

---

[5] Section 503B(b)(4) and (5) of the FD&C Act.
[6] Section 503B(d)(4)(C) of the FD&C Act.
[7] Section 503B(a)(2)(A) of the FD&C Act.
[8] 21 CFR 207.3.
[9] Section 503B(a)(2) of the FD&C Act and 21 CFR 207.1.
[10] Inactive ingredients are not subject to section 503B(a)(2) of the FD&C Act and will not be included in the 503B Bulks List because they are not included within the definition of a bulk drug substance. Pursuant to section 503B(a)(3), inactive ingredients used in compounding must comply with the standards of an applicable United States Pharmacopeia or National Formulary monograph, if a monograph exists.

II. Methodology for Developing the 503B Bulks List

A. Process for Developing the List

In the *Federal Register* of December 4, 2013 (78 FR 72838), FDA requested nominations for specific bulk drug substances for the Agency to consider for inclusion on the 503B Bulks List. In response to that request, interested groups and individuals nominated a wide variety of substances. However, many of those nominations were not for substances used in compounding as active pharmaceutical ingredients or did not include sufficient information to allow FDA to evaluate the nominated substance. To improve the efficiency of the process for the development of the list of bulk drug substances, FDA reopened the nomination process in the *Federal Register* of July 2, 2014 (79 FR 37750), and provided more detailed information on what it needs to evaluate nominations for the list. On October 27, 2015 (80 FR 65770), the Agency opened a new docket, FDA-2015-N-3469, to provide an opportunity for interested persons to submit new nominations of bulk drug substances or to re-nominate substances with sufficient information.

As FDA evaluates bulk drug substances, it intends to publish notices for public comment in the *Federal Register* that describe its proposed position on each substance along with the rationale for that position.[11] After considering any comments on FDA's proposals regarding whether to include nominated substances on the 503B Bulks List, FDA intends to consider whether input from the Pharmacy Compounding Advisory Committee (PCAC) on the nominations would be helpful to the Agency in making its determination, and if so, it will seek PCAC input.[12] Depending on its review of the docket comments and other relevant information

[11] This is consistent with procedure set forth in section 503B(a)(2)(A)(i). Although the statute only directs FDA to issue a *Federal Register* notice and seek public comment when it proposes to include bulk drug substances on the 503B Bulks List, we intend to seek comment when the Agency has evaluated a nominated substance and proposes either to include or not to include the substance on the list.

[12] Section 503B does not require FDA to consult the PCAC before developing a 503B Bulks List.

before the Agency, FDA may finalize its proposed determination without change, or it may finalize a modification to its proposal to reflect new evidence or analysis regarding clinical need. FDA will then publish in the *Federal Register* a list identifying the bulk drug substances for which it has determined there is a clinical need and FDA's rationale in making that final determination. FDA will also publish in the *Federal Register* a list of those substances it considered but found that there is no clinical need to use in compounding and FDA's rationale in making this decision.

FDA intends to maintain a current list of all bulk drug substances it has evaluated on its website, with separate lists for bulk drug substances it has placed on the 503B Bulks List and those it has decided not to place on the 503B Bulks List. FDA will only place a bulk drug substance on the 503B Bulks List where it has determined there is a clinical need for outsourcing facilities to compound drug products using the bulk drug substance. If a clinical need to compound drug products using the bulk drug substance has not been demonstrated, based on the information submitted by the nominator and any other information considered by the Agency, FDA will not place a bulk drug substance on the 503B Bulks List.

FDA intends to evaluate the bulk drug substances nominated for the 503B Bulks List on a rolling basis. FDA will evaluate and publish in the *Federal Register* its proposed and final determinations in groups of bulk drug substances until all nominated substances that were sufficiently supported have been evaluated and either placed on the 503B Bulks List or identified as bulk drug substances that were considered but determined not to be appropriate for inclusion on the 503B Bulks List. [13]

[13] On June 10, 2016, FDA announced the availability of a guidance for industry that provides additional information regarding FDA's policies for bulk drug substances nominated for the 503B Bulks List pending our review of nominated substances under the "clinical need" standard entitled "Interim Policy on Compounding Using Bulk Drug

B. Analysis of Substances Nominated for the List

As noted above, the 503B Bulks List will include bulk drug substances for which there is a clinical need. The Agency is beginning its evaluation of some of the bulk drug substances that were nominated for inclusion on the 503B Bulks List, proceeding case by case, under the standard provided by the statute. [14] In applying this standard to develop the proposals in this notice, FDA is interpreting the phrase "bulk drug substances for which there is a clinical need" to mean that the 503B Bulks List may include a bulk drug substance if: (1) there is a clinical need for an outsourcing facility to compound the drug product and (2) the drug product must be compounded using the bulk drug substance. FDA is not interpreting supply issues, such as backorders, to be within the meaning of "clinical need" for compounding with a bulk drug substance. Section 503B separately provides for compounding from bulk drug substances under the exemptions from the FD&C Act discussed above if the drug product compounded from the bulk drug substance is on the FDA drug shortage list at the time of compounding, distribution, and dispensing. Additionally, we are not considering cost of the compounded drug product as compared with an FDA-approved drug product to be within the meaning of "clinical need."

The bulk drug substances that we are addressing in this notice are components of FDA-approved drug products, and we therefore began our evaluation by asking the following questions:

Substances Under Section 503B of the Federal Food, Drug, and Cosmetic Act" (81 FR 37502); available at https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM469122.pdf.

[14] On March 26, 2018, FDA announced the availability of a draft guidance entitled "Evaluation of Bulk Drug Substances Nominated for Use in Compounding Under Section 503B of the Federal Food, Drug, and Cosmetic Act" (503B Bulks Evaluation Guidance) (83 FR 12952); available at https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM602276.pdf. The draft guidance proposes policies for developing the 503B Bulks List, including the interpretation of the phrase "bulk drug substances for which there is a clinical need," as it is used in section 503B. The Agency is considering comments it received on this draft guidance and is working to finalize the guidance.

(a) Is there a basis to conclude, for each FDA-approved product that includes the nominated bulk drug substance, that (i) an attribute of the FDA-approved drug product makes it medically unsuitable to treat certain patients for a condition that FDA has identified for evaluation, and (ii) the drug product proposed to be compounded is intended to address that attribute?

(b) Is there a basis to conclude that the drug product proposed to be compounded must be produced from a bulk drug substance rather than from an FDA-approved drug product?

The reason for question (a) is that unless an attribute of the FDA-approved drug is medically unsuitable for certain patients, and a drug product compounded using a bulk drug substance that is a component of the approved drug is intended to address that attribute, there is no clinical need to compound a drug product using that bulk drug substance. Rather, such compounding would unnecessarily expose patients to the risks associated with drug products that do not meet the standards applicable to FDA-approved drug products for safety, effectiveness, quality, and labeling and would undermine the drug approval process. The reason for question (b) is that to place a bulk drug substance on the 503B Bulks List, FDA must determine that there is a clinical need for outsourcing facilities to compound a drug product *using the bulk drug substance* rather than starting with an FDA-approved drug product.

If the answer to both of these questions is "yes," there may be clinical need for outsourcing facilities to compound using the bulk drug substance, and we would analyze the question further.[15] If the answer to either of these questions is "no," we generally would not include the bulk drug substance on the 503B Bulks List, because there would not be a basis to

[15] According to FDA's proposal in its 503B Bulks Evaluation Guidance, the additional analysis would consist of the application of four additional factors. We did not answer "yes" to both of the threshold questions for bumetanide, nicardipine hydrochloride, or vasopressin, and we did not consider these four additional factors in our proposal not to include bumetanide, nicardipine hydrochloride, or vasopressin on the 503B Bulks List.

conclude that there may be a clinical need to compound drug products using the bulk drug substance instead of administering or starting with an approved drug product.

III. Substances Proposed for the 503B Bulks List

The three bulk drug substances that have been evaluated to date and that FDA is proposing not to place on the list, and the reasons for those proposals, are as follows:

1. Bumetanide

Bumetanide has been nominated for inclusion on the 503B Bulks List to compound a drug product that manages edema associated with congestive heart failure, cirrhosis, and renal disease.[16] The proposed route of administration is intravenous infusion, the proposed dosage form is injection, and the proposed strength is 0.1 milligrams per milliliter (mg/mL). The nominated bulk drug substance is a component of FDA-approved drug products (e.g., ANDAs 074332 and 079196). FDA-approved bumetanide is available as a 0.25 mg/mL injection that may be administered parenterally (intravenously or intramuscularly) to patients in whom gastrointestinal absorption may be impaired or in whom oral administration is not practical.[17,18]

Because bumetanide is a component of an FDA-approved drug product, we considered whether there is a basis to conclude that the drug product proposed to be compounded must be compounded using a bulk drug substance. The nomination does not provide a basis to conclude that a bulk drug substance must be used to prepare a drug product containing bumetanide at concentrations below the concentration of the FDA-approved drug product (0.25 mg/mL). The nomination states that it may not be safer to prepare a drug product at such concentrations by starting with the approved drug; however, the nomination also recognizes that doing so would

[16] See Docket No. FDA-2015-N-3469, document no. FDA-2015-N-3469-0013.
[17] See, e.g., labeling available as of the date of this notice at https://www.accessdata.fda.gov/spl/data/f983b4df-996d-4558-adf7-ee4be1b3a03a/f983b4df-996d-4558-adf7-ee4be1b3a03a.xml.
[18] Bumetanide is also approved as an oral tablet. See, e.g., ANDA 074225.

only require a dilution. It does not take the position or provide support for a position that a bulk drug substance must be used to prepare these concentrations of bumetanide.[19,20]

Accordingly, FDA finds no basis to conclude that the drug products proposed to be compounded at a lower concentration than FDA-approved bumetanide must be compounded using a bulk drug substance rather than the approved drug product. We also find no basis to conclude that there is a clinical need for an outsourcing facility to compound a drug product using the bulk drug substance bumetanide and, therefore, we propose to not include bumetanide on the 503B Bulks List.

Because we are proposing not to include bumetanide on the 503B Bulks List for this reason, we do not consider question (a) in the analysis described above--whether an attribute of the FDA-approved drug product makes it medically unsuitable to treat certain patients and whether the drug product proposed to be compounded is intended to address that attribute.

2. Nicardipine Hydrochloride

Nicardipine hydrochloride has been nominated for inclusion on the 503B Bulks List.[21] The proposed route of administration is intravenous, the proposed dosage form is injection, and the proposed strength is 0.1-2.5 mg/mL. This nominated bulk drug substance is a component of FDA-approved drug products (e.g., NDAs 022276 and 019734). FDA has approved nicardipine

[19] For example, the nomination does not take the position or provide support for a position that a drug product prepared by starting with the approved drug would be unsuitable for administration.

[20] The nomination also states that bumetanide should be added to the 503B Bulks List because compounding from the bulk drug substance could allow outsourcing facilities to address issues such as drug shortages, product accessibility, and/or affordability. As noted above, section 503B contains a separate provision for compounding from bulk drug substances to address a drug shortage, and we do not interpret the other price- and supply-related reasons advanced by the nomination to fall within the statutory definition of "clinical need."

[21] See Docket No. FDA-2015-N-3469, document no. FDA-2015-N-3469-0002.

hydrochloride drug products as 0.1 mg/mL and 0.2 mg/mL ready-to-use solutions for intravenous administration and as a 2.5 mg/mL single-dose vial that must be diluted prior to infusion.[22,23]

Because nicardipine hydrochloride is a component of an FDA-approved drug product, we considered whether there is a basis to conclude that the drug product proposed to be compounded must be compounded using a bulk drug substance. The nomination does not provide a basis to conclude that a bulk drug substance must be used to prepare drug products containing nicardipine hydrochloride at concentrations at or below the concentrations of the FDA-approved products (0.1, 0.2, and 2.5 mg/mL) and for the same route of administration (intravenous) as that described in the approved drug product labeling. Initially, we note that two nicardipine drug products are approved in ready-to-administer form (e.g., no further dilutions needed) at concentrations within the range described in the nominations. The nomination does not present a reason to compound a drug product from a bulk drug substance at these concentrations. With respect to other concentrations, the nomination asserts, without support, that it would be safer to use a bulk drug substance than to start with the approved drug product. However, the nomination does not take the position or provide support for the position that a bulk drug substance must be used to prepare these concentrations of nicardipine hydrochloride.[24] In fact, the approved labeling of another nicardipine hydrochloride drug product directs the drug product to be diluted to a concentration within that range.[25]

---

[22] See, e.g., labeling available as of the date of this notice at https://www.accessdata.fda.gov/spl/data/32756b4e-a977-47ac-9620-0c1ed74d7606/32756b4e-a977-47ac-9620-0c1ed74d7606.xml (ready-to-administer) and https://www.accessdata.fda.gov/spl/data/5444784f-fefe-4352-afd1-b4c487165f3a/5444784f-fefe-4352-afd1-b4c487165f3a.xml (for dilution).

[23] Nicardipine hydrochloride is also approved as an oral capsule. See, e.g., ANDA 074642.

[24] For example, the nomination does not take the position or provide support for a position that a drug product prepared by starting with the approved drug product would be unsuitable for patient administration.

[25] The nomination also states that nicardipine hydrochloride should be added to the 503B Bulks List because compounding from bulk could help outsourcing facilities to address drug shortages and inconsistencies in supply of generic injections. As noted in section II., section 503B of the FD&C Act already provides for compounding from

Accordingly, FDA finds no basis to conclude that the drug products proposed to be compounded at a concentration at or lower than FDA-approved nicardipine hydrochloride must be compounded using a bulk drug substance rather than the approved drug product. We also find no basis to conclude that there is clinical need for an outsourcing facility to compound using the bulk drug substance nicardipine hydrochloride and, therefore, we propose to not include nicardipine hydrochloride on the 503B Bulks List. Because we are proposing not to include nicardipine hydrochloride on the 503B Bulks List for this reason, we do not consider question (a) in the analysis described above--whether an attribute of the FDA-approved drug product makes it medically unsuitable to treat certain patients and whether the drug product proposed to be compounded is intended to address that attribute.

3. Vasopressin

Vasopressin was nominated for inclusion on the 503B Bulks List to compound a drug product that treats septic shock, post-cardiotomy shock, diabetes insipidus, and hypotension.[26] The proposed route of administration is intravenous; the proposed dosage form is injection. The nominators proposed a range of specific concentrations (0.1, 0.2, 0.4, and 1 units/mL (U/mL)), and also concentrations above that of the approved drug product without identifying any specific concentration. This nominated bulk drug substance is the active ingredient of the FDA-approved drug VASOSTRICT (NDA 204485). VASOSTRICT is approved as a 20 U/mL intravenous infusion that, per its labeling, should be diluted with normal saline or 5 percent dextrose in water to either 0.1 U/mL or 1 U/mL for intravenous administration.[27]

---

bulk drug substances to address a drug shortage, and we do not interpret the other price- and supply-related reasons stated in the nomination to constitute clinical need.

[26] See Docket No. FDA-2015-N-3469, documents nos. FDA-2015-N-3469-0012 and -0023.

[27] The labeling as of the date of this notice is available at https://www.accessdata.fda.gov/spl/data/4166e423-659e-4fe4-8a3c-2394434d00dd/4166e423-659e-4fe4-8a3c-2394434d00dd.xml.

Because vasopressin is a component of an FDA-approved drug product, we considered the nominations under questions (a) and (b) of the analysis described previously.

One of the nominations proposes vasopressin for the 503B Bulks List so that it can be used to compound a drug product whose concentration of vasopressin is higher than undiluted VASOSTRICT. The nomination does not identify an attribute of VASOSTRICT that makes it medically unsuitable for patients and that such high-concentration products are intended to address. The nomination does not identify any data or information as to the need for a higher concentration than the approved product, nor does the nomination identify specific higher concentrations it proposes to compound. In addition, the information provided in the nomination does not identify patients for whom a concentration at or below 20 U/mL is medically unsuitable and who would therefore require a higher concentration, and FDA is not aware of patients who would need concentrations above 20 U/mL.

Both nominations propose vasopressin for the 503B Bulks List so that it can be used to compound drug products whose concentrations of vasopressin are lower than undiluted VASOSTRICT. The nominations do not provide a basis to conclude that a bulk drug substance must be used to prepare a drug product that contains vasopressin at concentrations below the concentration of VASOSTRICT (20 U/mL) and uses the same diluents (dextrose and sodium chloride) and the same route of administration (intravenous) as that described in the approved product labeling. The nominations do not take the position or provide support for the position that a bulk drug substance rather than the FDA-approved drug product must be used to prepare these lower concentrations of vasopressin.[28] In fact, VASOSTRICT's approved labeling directs

[28] For example, the nomination does not take the position or provide support for a position that a drug product prepared by starting with the approved drug product would be unsuitable for patient administration.

VASOSTRICT to be diluted using the diluents described in the nominations to concentrations within which the drug products proposed to be compounded fall.[29]

Accordingly, FDA finds no basis to conclude that an attribute of VASOSTRICT makes it medically unsuitable to treat patients such that patients would need a higher concentration higher than that of VASOSTRICT. FDA also finds no basis to conclude that the drug products proposed to be compounded at a lower concentration than VASOSTRICT must be compounded using a bulk drug substance rather than the approved drug. Further, we find no basis to conclude that there is a clinical need for an outsourcing facility to compound using the bulk drug substance vasopressin and, therefore, we propose to not include vasopressin on the 503B Bulks List.

Dated: August 23, 2018.

Leslie Kux,

Associate Commissioner for Policy.

[29] One of the nominations also states that vasopressin should be added to the 503B Bulks List because compounding from the bulk drug substance could allow outsourcing facilities to address issues such as drug shortages, product accessibility, and/or affordability. As noted above, section 503B contains a separate provision for compounding from bulk drug substances to address a drug shortage, and we do not interpret the other price- and supply-related reasons advanced by the nomination to fall within the statutory definition of "clinical need."

[FR Doc. 2018-18614 Filed: 8/27/2018 8:45 am; Publication Date: 8/28/2018]